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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,918	12/28/2001	Rajiv Shah	047711-0293	2208

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EXAMINER

PAK, YONG D

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/035,918

Applicant(s)

SHAH ET AL.

Examiner

Yong D. Pak

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 April 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-8 and 10-54 is/are pending in the application.
- 4a) Of the above claim(s) 25-43 and 48-54 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-8,10-24 and 44-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>4/19/2005</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The amendment filed on April 19, 2005, amending claims 1, 10 and 46, has been entered.

Claims 1, 3-8 and 10-54 are pending. Claims 25-43 and 48-54 are withdrawn.
Claims 1, 3-8, 10-24 and 44-47 are under consideration.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on April 19, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

Applicant's amendment and arguments filed on April 19, 2005 have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 3-8, 19-24 and 44-47 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase "colonies have desired peroxide resistant properties". Colonies having "desired" properties conveys that the colonies having peroxide resistant properties are "wished for" or "longed for" and do not necessarily have "peroxide resistant properties". Examiner requests clarification of the above phrase.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 8, 19-24 and 44-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al. and Current Protocols in Molecular Biology.

Claims 1, 3-5, 8, 19-24 and 44-47 are drawn to a method of formulating a glucose oxidase that are resistant to degradation by hydrogen peroxide comprising generating a library of mutated glucose oxidase genes by PCR, screening colonies containing active glucose oxidase having resistance to degradation by peroxide and testing for active glucose oxidase via fluorescence. Claims 46-47 are drawn to a method of formulating a glucose oxidase and testing for glucose oxidase activity in a sensor.

Valdes et al. (form PTO-892) teaches that glucose oxidases in glucose sensors degrade over time due to hydrogen peroxide. One of ordinary skill in the art would recognize usefulness of mutant glucose oxidases that are resistant to peroxide degradation and thereby generate such mutants with recombinant skills well known in the art.

The difference between the reference of Valdes et al. and the instant claims is that the reference of Valdes et al. does not teach a method of generating mutant glucose oxidase genes and screening for mutated glucose oxidases which are resistant to degradation in the presence of hydrogen peroxide.

However, methods in generating random mutagenesis via PCR and screening for mutant having desired properties are very well known. *Current Protocols in Molecular Biology* (form PTO-892 – reference is also available on-line at http://www.mrw.interscience.wiley.com/cp/cpmb/cpmb_contents_fs.html) teaches many

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different protocols in generating a library of mutated glucose oxidase genes via error-prone PCR and gene shuffling, screening, selecting and isolating mutated genes and expression of the mutant protein (Chapter 3, 5-6, 8 and 10). The reference also teaches how to test for activity of the mutated protein and measuring concentrations of the isolated proteins, such as fluorescence (Chapter 10 and Appendix 3H). Upon determining genes encoding active glucose oxidase, it would have been obvious to one of ordinary skill in the art to incubate colonies comprising said genes with hydrogen peroxide and determine if the encoded protein retain enzymatic activity, indicating their resistance to hydrogen peroxide.

Therefore, combining the teachings of the above two references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to mutagenize the glucose oxidase gene of Valdes et al. One of ordinary skill in the art would have been motivated to mutagenize the protein in order to screen for mutants which are able to retain enzymatic activity in glucose sensors in the presence of hydrogen peroxide. One of ordinary skill in the art would have had a reasonable expectation of success in making mutant glucose oxidases resistant to peroxide degradation since Current Protocols in Molecular Biology demonstrates the success of random mutagenesis employing different PCR techniques and teaches different methods of screening, selecting and isolating the mutated gene and its encoded protein and since Valdes et al. teaches that the degradation of glucose oxidase in glucose sensors is due to hydrogen peroxide.

Therefore, Valdes et al. and Current Protocols in Molecular Biology render claims 1, 3-5, 8, 19-24 and 44-47 *prima facie* obvious to those skilled in the art.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that neither of the cited references describe or suggest formulation a glucose oxidase enzyme by mutating glucose oxidases to make them resistant peroxide degradation because Valdes et al. provides no suggestion or motivation to mutate glucose oxidases to make them resistant to peroxide degradation, but only discusses the degradation effects of peroxide on glucose oxidase and makes no attempt to solve the problem. Examiner respectfully disagrees. There is suggestion or motivation to combine and modify the cited references. Valdes et al. teaches a problem with glucose sensors, that the enzyme used to detect glucose, glucose oxidase, degrades over time due to peroxide degradation. One of ordinary skill in the art would recognize this problem, degradation of glucose oxidase, and thereby decreasing the sensor's ability to quantify glucose levels, and would have been motivated to reduce degradation of glucose oxidase, either by removing or neutralizing peroxide or using mutants which are resistant to peroxide. Therefore, Valdes et al. provide motivation to either remove peroxide or use mutant glucose oxidases resistant to peroxide, which are made using techniques known in the art, as taught by *Current Protocols in Molecular Biology*.

Applicants argue that one of ordinary skill in the art would have addressed the peroxide degradation by removing peroxide and not using mutant glucose oxidase.

Examiner respectfully disagrees. While at one time one of ordinary skill in the art would have addressed the peroxide degradation by such methods, the art of biotechnology is constantly changing. Methods in generating random mutagenesis via PCR and screening for mutant having desired properties are very well known and have been widely practiced, as taught by *Current Protocols in Molecular Biology*. Therefore, Valdes et al. and *Current Protocols in Molecular Biology* in combination provide motivation to formulate or make glucose oxidase mutants resistant to peroxide degradation.

Applicants also argue that *Current Protocols in Molecular Biology* does not provide teaching or suggestion of creating a library of mutated glucose oxidase genes and of screening colonies for peroxide resistant properties. Examiner respectfully disagrees. Applicants are reminded that the rejection is based on the combination of Valdes et al. and *Current Protocols in Molecular Biology*. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The references in combination provide motivation to formulate peroxide resistant glucose oxidase for reasons discussed above.

Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al. and Current Protocols in Molecular Biology as applied to claims 1, 3-5, 8, 19-24 and 44-47 above, and further in view of Aldrich Catalog.

Claims 6-7 are drawn to a method of formulating glucose oxidase by generating a library of mutated glucose oxidase genes and determining if colonies have active glucose oxidase by fluorescence.

The combined teachings of Valdes et al. and Current Protocols in Molecular Biology as applied to claims 1, 3-5, 19-24 and 44-47, teach a method of formulating a glucose oxidase with decreased degradation in the presence of hydrogen peroxide, as discussed above.

The difference between the teachings of the two references and the claimed invention is that the two references do not teach a method of using leuco-crystal-violet.

However, In the state of the art, there are many known colored products that can be used, including Leo Crystal Violet available through Aldrich (Aldrich Catalog 1998-1999 – cited on previous PTO-892).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use fluorescence technique to screen for active galactose oxidases. The motivation of screening colonies having active galactose oxidase is to efficiently screen for the mutant enzymes instead of isolating and purifying enzymes. One of ordinary skill in the art would have had a reasonable expectation of success since leuco-crystal-violets are routinely used in the art in fluorescence assays.

Therefore, combining the teachings of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use Leo Crystal Violet to screen for mutant glucose oxidase that are enzymatically active. One of ordinary skill in the art would have been motivated to use color changing substances to readily determine active glucose oxidases. One of ordinary skill in the art would have had a reasonable expectation of success in screening for mutant active glucose oxidase since *Current Protocols in Molecular Biology* teaches methods of determining proteins have enzymatic activity using fluorescence.

Therefore, Valdes et al., *Current Protocols in Molecular Biology* and Aldrich render claims 6-7 *prima facie* obvious to those skilled in the art.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the cited references to not alone or in combination provide suggestion or motivation of mutating glucose oxidase genes or screening for colonies of glucose oxidase for peroxide resistance. As discussed above, Valdes et al. and *Current Protocols in Molecular Biology* in combination provides motivation or suggestion for making glucose oxidase resistant to peroxide degradation.

Regarding the reference of Wohlfarht et al., Examiner inadvertently included citation of Wohlfarht et al.

Applicants discuss many advantages of the present invention and argues that had the presently claimed method been obvious over the prior art of record, then such

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significant advantages would have led the authors of those prior art references to at least mention the possibility of performing such method and thereby showing the present invention to be not obvious of the prior art of record. Examiner respectfully disagrees. Requirements of non-obviousness is based on determining whether the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made, and not when the cited references were published.

At the time the invention was made, the level of skill in the art in mutating enzymes having desired functional properties was much more advanced than when Valdes et al. was published, allowing a wide solution for reducing degradation of glucose oxidase, by removing or neutralizing peroxide or by using mutant glucose oxidase resistant to peroxide.

Hence the rejection is maintained.

None of the claims are allowable.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner



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